The Effect of Halothane on Ventricular Automaticity

Joseph R. Logic, M.D., Ph.D.,* and Dean H. Morrow, M.D.†

The effects of halothane on ventricular automaticity were studied in ten dogs anesthetized with sodium pentobarbital. Halothane (1–2 per cent in oxygen) consistently depressed ventricular escape pacemaker activity during supramaximal right vagal stimulation, as demonstrated by prolongation of the ventricular escape time 6.8 ± 1.31 sec and slowing of the average idioventricular escape rate 7.4 ± 1.92 beats min^{-1}. Similarly, halothane suppressed ectopic pacemaker activity and markedly decreased ventricular automaticity in dogs given a toxic dose of ouabain. The latter effects were concomitant with prompt conversion of glycoside-induced ventricular tachycardia to sinus rhythm. The halothane effect on pacemaker activity was markedly greater when the dog had received ouabain. This observation suggests differences between membrane activities of halothane in normal and ouabain-treated animals. Suppression of pacemaker activity undoubtedly contributes to the antiarrhythmic effect of halothane. (Key words: Halothane; Ventricular automaticity; Pacemaker.)

PREVIOUS STUDIES from this laboratory have demonstrated the ability of halothane to suppress experimentally-induced ventricular tachyarrhythmias, as shown by the conversion of ouabain-induced ventricular tachycardia to sinus rhythm during intermittent exposures to halothane in oxygen.[1, 2] In addition, the ability of halothane to antagonize ouabain toxicity was shown to be effective at cumulative ouabain doses approaching the lethal toxic dose in the dog.[1] We recently documented the ability of halothane to restore normal sinus rhythm when idioventricular tachycardia had developed during the evolution of experimental myocardial infarction in the dog.[3] It was particularly noteworthy in that study that the arrhythmia was suppressed despite concomitant slowing of the supraventricular pacemaker by the anesthetic agent. Since this arrhythmia probably represents ischemia-related acceleration of pacemaker activity in the conducting fibers in the ventricle,[2] it seemed important to assess more directly the effect of halothane on the physiologic ventricular escape mechanisms and to compare those results with its effects on the alterations of ventricular automaticity induced by toxic amounts of ouabain.

Methods

Subjects of the study were ten conditioned mongrel dogs, body weights 11.1 ± 1.29 (SE) kg, anesthetized with pentobarbital sodium 20–30 mg/kg, iv. A polyethylene cannula was inserted into one femoral artery to record arterial blood pressure with a Statham P 23Ad transducer and to obtain arterial samples for periodic measurement of P_{O_2} (range 523–577 torr), P_{CO_2} (range 28.9–35.7 torr), and *p*H. All infusions were made into a similarly cannulated femoral vein. Respiration was controlled with an anesthetic ventilator through a cuffed endotracheal tube, using 100 per cent oxygen. Minute ventilation was adjusted as needed to maintain arterial *p*H at approximately 7.4 (range 7.40–7.45). Temperature was maintained at 38 C by application of external heat. Lead II of the electrocardiogram (ECG) was recorded with phasic arterial pressure at appropriate paper speeds on a multichannel direct-writing thermal recorder.

Ventricular automaticity was assessed by determining the ventricular escape time (V.E.T.) in seconds and the average idioventricular escape rate (V.E.R.) in beats min^{-1} during supramaximal stimulation of the distal end of the sectioned right vagus, using a Grass S-4 stimu-

* Assistant Professor. Part of this work was performed during an Advanced Research Fellowship, American Heart Association.
† Professor of Anesthesiology and Pharmacology. Career Development Awardee, GM-33,544 from the National Institutes of Health.
Received from the Departments of Medicine and Anesthesiology, University of Kentucky College of Medicine, Lexington, Kentucky, and the Division of Clinical Physiology, University of Tennessee Medical Units, Memphis, Tennessee. Accepted for publication August 3, 1971. Supported in part by grant NB-08331 from the National Institute of Neurological Disease and Blindness.

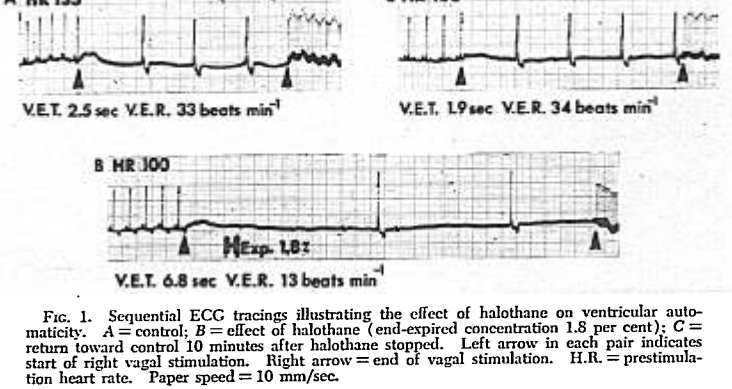

FIG. 1. Sequential ECG tracings illustrating the effect of halothane on ventricular automaticity. *A* = control; *B* = effect of halothane (end-expired concentration 1.8 per cent); *C* = return toward control 10 minutes after halothane stopped. Left arrow in each pair indicates start of right vagal stimulation. Right arrow = end of vagal stimulation. H.R. = prestimulation heart rate. Paper speed = 10 mm/sec.

TABLE 1. Effect of Halothane on Ventricular Automaticity

Experiment	Ventricular Escape Time (V.E.T.) (Sec)	Ventricular Escape Rate (Beats Min⁻¹)	ΔV.E.T.	ΔV.E.R.	Blood Pressure (torr)	Heart Rate (Beats Min⁻¹)
3A. Control	18.6	11.5			164/116	180
Halothane	23.8	7.7	5.2	−3.8	95/68	138
3B. Control	18.3	13.8			152/108	160
Halothane	23.8	7.7	5.5	−6.1	80/68	149
4. Control	1.8	32.4			140/100	144
Halothane	17.9	19.9	16.1	−12.5	70/43	132
5. Control	5.3	19.6			144/105	187
Halothane	10.4	15.0	5.5	−4.6	91/66	142
6. Control	17.7	19.3			155/110	180
Halothane	25.0	14.6	7.3	−4.7	130/92	164
7A. Control	10.2	20.7			116/80	188
Halothane	14.0	15.8	3.8	−4.9	84/52	192
7B. Control	11.8	19.3			108/78	210
Halothane	21.3	15.0	9.5	−4.3	90/38	230
11. Control	2.5	33.0			150/80	133
Halothane	6.8	13.1	4.3	−19.9	80/55	106
12. Control	29.5	13.8			140/104	164
Halothane	33.5	10.2	3.8	−3.6	100/78	142
Mean difference			6.8	−7.4		
SE			± 1.31	± 1.92		
P			<0.001	<0.05		

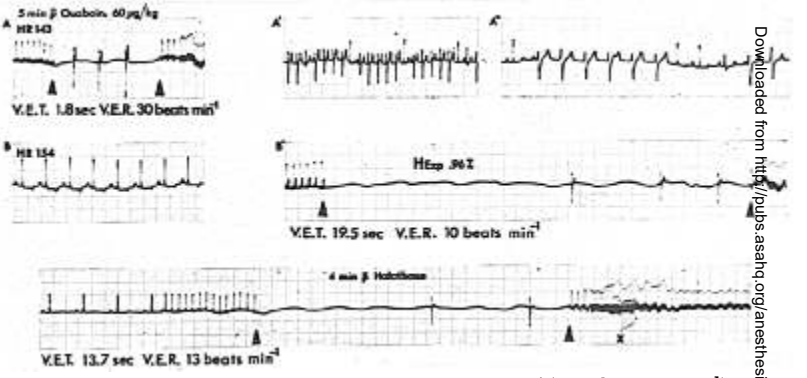

FIG. 2. Effect of halothane on ventricular automaticity enhanced by ouabain; arrows indicate duration of right vagal stimulation. *A*: 5 minutes after 60 μg/kg ouabain, V.E.T. (ventricular escape time) = 1.8 sec at V.E.R. (ventricular escape rate) 30 beats min^{-1}. A′ and A″ (speed 25 mm/sec) are continuous tracings showing the progressive development of an ectopic ventricular tachycardia (rate about 150/min) approximately 6 minutes after ouabain. V.E.T. at this time was unobtainable. *B*: Conversion of the ventricular tachycardia to normal sinus rhythm after 7 minutes of 1 per cent halothane. *B′* illustrates prolongation of the V.E.T. to 19.5 sec at an escape rate of 10 beats min^{-1} after 7.5 minutes of exposure to halothane. *C*: Return toward control 4 minutes after stopping halothane, V.E.T. decreased to 13.7 sec, with a slightly accelerated escape rate of 13 beats min^{-1}. Note reappearance of ectopic beats at *x* during withdrawal of antiarrhythmic halothane effect. Paper speed = 10 mm/sec.

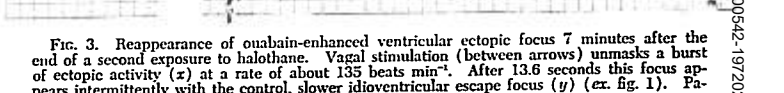

FIG. 3. Reappearance of ouabain-enhanced ventricular ectopic focus 7 minutes after the end of a second exposure to halothane. Vagal stimulation (between arrows) unmasks a burst of ectopic activity (*x*) at a rate of about 135 beats min^{-1}. After 13.6 seconds this focus appears intermittently with the control, slower idioventricular escape focus (*y*) (*ex.* fig. 1). Paper speeds, left panel 25 mm/sec, right panel 5 mm/sec.

lator and stimulus isolation unit according to a modification of the technique described by Helfant *et al.*[4] V.E.T. was defined as the time from the onset of stimulation to the first ventricular escape beat during vagally-induced supraventricular asystole, while V.E.R. was the average frequency per minute of the escape focus during continued vagal stimulation. Frequency and voltage of stimulation were varied in each experiment in order to produce sinoatrial and atrioventricular block during each stimulation period. In seven dogs ouabain was infused intravenously in doses ranging from 36 to 60 μg/kg in order to produce sustained ventricular tachyarrhythmia. In each experiment delivered concentrations of 1–2 per cent halothane in oxygen were intermittently introduced and ventricular automaticity was assessed at 5–10-minute intervals. End-expiratory halothane concentrations were determined at appropriate intervals, using a Mayo Vapor Analyzer.

Results

Effects of Halothane on V.E.T. and V.E.R.

V.E.T. differed in different dogs, but was always reproducible within 1–2 seconds in individual experiments.[4] There was a clear re-

TABLE 2. Comparison of the Maximum Halothane Effects on Ventricular Automaticity before and after Ouabain

Experiment	ΔV.E.T. (Sec)	ΔV.E.R. (Beats Min^{-1})	Blood Pressure (torr)	Heart Rate (Beats Min^{-1})
3. Control	5.5	−6.1	80/68	140
Ouabain	21.5	−9.0	103/65	138
5. Control	5.5	−4.6	91/66	142
Ouabain	31.9	−10.4	103/65	138
6. Control	7.3	−4.7	130/92	164
Ouabain	20.6	−13.3	136/90	160
7. Control	9.5	−4.3	90/38	230
Ouabain	18.7	−9.0	132/100	188
12. Control	3.8	−3.6	100/78	142
Ouabain	9.4	−7.8	108/84	134
Summary				
Control (± SE)	6.3 ± 0.97	−4.7 ± 0.34		
Ouabain (± SE)	20.5 ± 3.59	−9.9 ± 2.98		
Difference: *P*	<0.02	>0.05		

lationship between average V.E.R. and duration of V.E.T. in every dog, with the longest V.E.T. invariably being accompanied by the slowest V.E.R. With the conditions of stimulation used in these experiments, supraventricular escape pacemakers were not usually observed. Figure 1 shows the prolongation of V.E.T. and slowing of V.E.R. during exposure to halothane (*B*) and the prompt return to control with similar supraventricular rates following termination of the anesthesia (*C*) in a typical experiment. In nine trials in seven dogs prior to any other intervention (table 1), halothane increased V.E.T. 6.8 ± 1.31 sec ($P < 0.0001$) and slowed V.E.R. 7.4 ± 1.92 beats min^{-1} ($P < 0.05$). The maximal slowing of V.E.T. at the peak of the halothane effect was quite variable, as shown in table 1.

EFFECT OF HALOTHANE AFTER OUABAIN

The first response observed following the administration of ouabain was a progressive shortening of the control escape pacemaker interval, accompanied by acceleration of V.E.R. We did not introduce halothane during this period. Prior to the development of significant ventricular tachycardia, however, a different, earlier, and progressively-accelerating ectopic focus appeared during vagal stimulation (fig. 2). It was this focus that ultimately increased its rate over that of the supraventricular pacemaker until it established bursts (fig. 2) and, finally, sustained ventricular tachycardia. When ventricular tachycardia became manifest, V.E.T. either was unobtainable or was essentially zero, with the ouabain-induced focus firing at rates of 150 to 220/min. This observation is similar to that reported by Helfant *et al.*[4] following administration of toxic amounts of acetylstrophanthidin to dogs. In our experiments, however, the early, rapid ectopic focus uncovered by vagal stimulation frequently slowed and disappeared after an initial burst of activity before clearly and persistently accelerating to become the dominant cardiac pacemaker. The electrophysiologic mechanisms for the development in pacemaker tissues of such extinction or exit blocks remain unknown.

Halothane restored sinus rhythm in every dog during outbain-induced tachycardia, and this was always associated with marked prolongation of V.E.T. and slowing of V.E.R. (fig. 2). The design of these experiments did not permit us to establish precise antiarrhythmic dose responses for halothane. In several trials, during the development of the maximal halothane effect or during its disappearance, vagal stimulation still revealed the presence of the accelerated ectopic focus and its extinc-

tion when halothane had restored sinus rhythm after ouabain (fig. 3). However, in every trial, when sinus rhythm had been re-established at the peak of the halothane effect, the dominant ventricular pacemaker during vagally-induced asystole was either the markedly slowed ouabain-enhanced ectopic focus (fig. 2) or, if it had been completely suppressed, the slowed control escape focus.

A consistent finding in five dogs in which identical exposures to halothane prior to and following toxic amounts of ouabain could be compared was the observation that halothane depressed V.E.T., and generally V.E.R., to a markedly greater degree whenever ouabain had been administered (table 2). The change in V.E.T. was significant with respect to control measurements made prior to administration of the glycoside ($P < 0.02$). The change in V.E.R. did not achieve statistical significance, although four of five dogs had at least twofold decreases in V.E.R.

Discussion

This study has extended our previous observations concerning the antiarrhythmic properties of halothane in ventricular tachyarrhythmias. It seems clear that V.E.T. and V.E.R., as used in this study, represent a valid expression of the inherent, latent automaticity and rhythmicity of the most rapid subnodal pacemaker in the intact heart. Since halothane always prolonged V.E.T. and slowed V.E.R. without altering the ECG morphology of the escape beat, our study documents the suppression of normal escape pacemaker activity by halothane and is consistent with the recent observations of Reynolds *et al.*,[5] showing halothane suppression of spontaneous phase 4 depolarization in Purkinje fibers *in vitro*.

The effectiveness of halothane in suppressing digitalis-induced ventricular tachycardia was again demonstrated. Since a recent study by Damato *et al.*[6] has shown that the site of the ectopic pacemaker in digitalis-induced ventricular tachycardia was in either the left bundle branch or the more distal Purkinje fibers, with retrograde activation of the bundle of His, this study documents that halothane was capable of suppressing glycoside enhancement of such ectopic pacemakers. Moreover, the study of Helfant *et al.*[4] showed that another antiarrhythmic agent, diphenylhydantoin sodium, markedly prolonged V.E.T. beyond control values after glycoside exposure, as was observed with halothane in this study.

The consistent observation that halothane suppressed both physiologic escape and ectopic pacemaker activity far more in the presence of ouabain was of great electrophysiologic interest. If, as appears to be the case, spontaneous depolarization in pacemaking fibers represents a time-dependent decrease in the conductance of the membrane for K^+ ions (gK^+),[7] then halothane must have altered the time-dependent conductance change in the electrically excitable membranes of pacemaker fibers. Such an effect would thus slow the inherent rate of pacemaking fibers. The marked changes in pacemaker activity seen whenever ouabain was administered in toxic amounts suggest that ouabain may influence pacemaker fiber ionic conductances in ways necessitating an even greater membrane-stabilizing effect of halothane and other antiarrhythmic membrane-active drugs before the time-dependent decrease in gK^+ can bring the pacemaker fiber to its critical threshold potential and initiate a propagated response.[7]

References

1. Morrow DH, Townley NT: Anesthesia and digitalis toxicity: An experimental study. Anesth Analg (Cleve) 43:510–519, 1964
2. Morrow DH, Knapp DE, Logic JR: Anesthesia and digitalis toxicity. V: Effect of the vagus on ouabain-induced ventricular automaticity during halothane. Anesth Analg (Cleve) 49: 23–27, 1970
3. Logic JR, Gatz RN, Morrow DH: Idioventricular tachycardia complicating experimental myocardial infarction. Dis Chest 56:477–480, 1969
4. Helfant RH, Scherlag BJ, Damato AN: The electrophysiological properties of diphenylhydantoin sodium as compared to procaine amide in the normal and digitalis-intoxicated heart. Circulation 36:108–118, 1967
5. Reynolds AK, Chiz JF, Pasquet AF: Halothane and methoxyflurane—a comparison of their effects on cardiac pacemaker fibers. ANESTHESIOLOGY 33:602–610, 1970
6. Damato AN, Lau SH, Bobb GA: Digitalis-induced bundle-branch ventricular tachycardia studied by electrode catheter recordings of the specialized conducting tissues of the dog. Circ Res 28:16–22, 1971
7. Vassale M: Analysis of cardiac pacemaker potential using a "voltage clamp" technique. Am J Physiol 210:1335–1341, 1966